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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,808	08/05/2003	Jean Rapin	10945.105004	8829

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EXAMINER	
CORDERO GARCIA, MARCELA M	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 05/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/635,808	Applicant(s) RAPIN ET AL.
	Examiner Marcela M Cordero Garcia	Art Unit 1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on April 15, 2005.

Claims 1, 3, 6 and 7 are pending in the application. Claims 1 and 3 are amended.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Claims 1, 3, 6 and 7 are presented for examination on the merits.

Response to Amendment

The amendment filed April 15, 2005 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows (See claim 1): "to a human patient thereof".

Applicant is required to cancel the new matter in the reply to this Office Action or to specifically point out within the disclosure support for this amendment.

With respect to the art rejections below, please note the following:

Alzheimer's disease, as referenced by Kan (Eur J Med Chem, 1992) is known in the art to be associated to brain lesions (amyloid B-protein plaques) whose density correlates with the severity of the disease and whose composition is toxic for mature

neurons and brain regions (see, e.g., page 565, column 2 and page 566, column 1). Therefore, based upon the reference teachings, Alzheimer's disease can be classified as a postlesional disease of toxic origin.

In addition, please note that amnesia, as referenced by http://www.smithsrisca.demon.co.uk/neuro-glossary.html (accessed online, October 4, 2004) is known in the art to be associated, inter alia, with bilateral lesions of either the hippocampal regions or the mammilla bodies, that may have originated by a mechanical or physical agent (trauma) (http://accessscience.com/, search term 'trauma', accessed online, October 4, 2004), and therefore can be classified as a postlesional disease of traumatic origin.

Ischemic heart disease may be caused, as is know in the art and referenced by Tedeshi et al. (US 6,645,518), by atherosclerotic lesions. Therefore ischemic heart disease can be classified as postlesional disease of ischemic origin.

Alzheimer's disease and amnesia are known in the art to be neurodegenerative disorders, as referenced by Henrichwark et al. (US 6,080,848).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 6 and 7 stand rejected under 35 U.S.C. 102(b) as being anticipated by Vandal (US 5,212,158). The instant claims are drawn to a method for the treatment of postlesional diseases of ischemic, traumatic or toxic origin, comprising administering an effective amount of a proline derivative of formula (I). A specific species for the method is, e.g., cinnamoyl-glycyl-L-phenylalanyl-L-prolinamide. Please note that the administered subject has not been defined and therefore the claims read upon administration to a subject not affected with any of the diseases.

Vandai beneficially teaches the use of the L-proline derivatives encompassing formula (I) for the treatment of postlesional disorders of toxic origin, such as Alzheimer's disease and of traumatic origin, such as amnesia (see, e.g., abstract and claims). Vandai teaches the species cinnamoyl-glycyl-L-phenylalanyl-L-prolinamide (see column 16, lines 13-15), and the administration of the L-proline derivative compounds to mice in order to treat amnesia (see example 9).

Applicant's arguments indicate that Vandai does not disclose or suggest a mechanism of action of the compounds and that the alleged disclosure of treatment of neurodegenerative diseases in Vandai does not anticipate or render obvious the amended claims to the treatment of postlesional diseases. Applicant's specifically point out that the invention of Vandai does not read upon the instantly claimed "method for the treatment of a postlesional disease of ischemic, traumatic or toxic origin <u>characterized by nerve cell necrosis</u> comprising administering an effective amount of a compound of formula (I)...". Applicant's arguments and exhibits have been carefully considered, but not deemed persuasive because (as stated above and in the previous

Office Action) Alzheimer's disease, as referenced by Kan (Eur J Med Chem, 1992) is known in the art to be associated to brain lesions (amyloid B-protein plaques) whose density correlates with the severity of the disease and whose composition is toxic for mature neurons and brain regions (see, e.g., page 565, column 2 and page 566, column 1), which inherently reads upon toxic nerve cell necrosis.

In addition, Applicant indicates that amnesia is not a postlesional disease of traumatic origin but a symptom. Applicant's arguments have been considered but not deemed persuasive because amnesia, as referenced by http://www.smithsrisca.demon.co.uk/neuro-glossary.html (accessed online, October 4, 2004) is known in the art to be associated, inter alia, with bilateral lesions of either the hippocampal regions or the mammilla bodies, that may have originated by a mechanical or physical agent (trauma) (http://accessscience.com/, search term 'trauma', accessed online, October 4, 2004), and therefore can be classified as a postlesional disease of traumatic origin, which inherently reads upon traumatic nerve cell necrosis. Amnesia is a term describing a group of disorders involving partial or total inability to remember past experiences (http://www.lef.org/protocols/prtcl-007.shtml, accessed online 04/05/05). Additionally, Applicant argues that the nootropic or even anti-neurodegenerative effect of special substances do not render their effect on regenerative processes obvious. Please note that, as drafted, the claims read upon a method of treatment of postlesional diseases characterized by necrotic cell death, which inherently read upon amnesia and Alzheimer's (see above).

Therefore, the reference is deemed to anticipate the instant claims above, as drafted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 6 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vandai (US 5,212,158). The instant claims are drawn to a method for the treatment of postlesional diseases comprising administering an effective amount of a proline derivative of formula (I). A specific species for the method is, e.g., cinnamoyl-glycyl-L-phenylalanyl-L-prolinamide.

Vandai beneficially teaches the use of the L-proline derivatives encompassing formula (I) for the treatment of postlesional disorders such as Alzheimer's disease and amnesia (see, e.g., abstract and claims). Vandai teaches the species cinnamoyl-glycyl-

L-phenylalanyl-L-prolinamide (see column 16, lines 13-15), and the administration of the L-proline derivative compounds to mice in order to treat amnesia (see example 9). It would have been obvious to one skilled in the art at the time that the invention was made to have used the compounds and methods taught by Vandai in the treatment of postlesional diseases such as amnesia and Alzheimer's disease, since the compounds and their activity in regards to such diseases were known as beneficially taught by Vandai. The adjustment of particular conventional working conditions (e.g., the selection of specific amino acid residues for R_1 and R_2 and X alkyl type substituents, the determination of a therapeutically effective amount to treat the specific diseases and/or the mode of administration) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Applicant's arguments indicate that Vandai does not disclose or suggest a mechanism of action of the compounds and that the alleged disclosure of treatment of neurodegenerative diseases in Vandai does not anticipate or render obvious the amended claims to the treatment of postlesional diseases. Applicant's specifically point out that the invention of Vandai does not read upon the instantly claimed "method for the treatment of a postlesional disease of ischemic, traumatic or toxic origin characterized by nerve cell necrosis comprising administering an effective amount of a compound of formula (I)...". Applicant's arguments and exhibits have been carefully considered, but not deemed persuasive because (as stated above and in the previous Office Action) Alzheimer's disease, as referenced by Kan (Eur J Med Chem, 1992) is known in the art to be associated to brain lesions (amyloid B-protein plaques) whose

density correlates with the severity of the disease and whose composition is toxic for mature neurons and brain regions (see, e.g., page 565, column 2 and page 566, column 1), which intrinsically reads upon toxic nerve cell necrosis.

In addition, Applicant indicates that amnesia is not a postlesional disease of traumatic origin but a symptom. Applicant's arguments have been considered but not deemed persuasive because amnesia, as referenced by http://www.smithsrisca.demon.co.uk/neuro-glossary.html (accessed online, October 4, 2004) is known in the art to be associated, inter alia, with bilateral lesions of either the hippocampal regions or the mammilla bodies, that may have originated by a mechanical or physical agent (trauma) (http://accessscience.com/, search term 'trauma', accessed online, October 4, 2004), and therefore can be classified as a postlesional disease of traumatic origin, which intrinsically reads upon traumatic nerve cell necrosis. Amnesia is a term describing a group of disorders involving partial or total inability to remember past experiences (http://www.lef.org/protocols/prtcl-007.shtml, accessed online 04/05/05). Additionally, Applicant argues that the nootropic or even anti-neurodegenerative effect of special substances do not render their effect on regenerative processes obvious. Please note that, as drafted, the claims read upon a method of treatment of postlesional diseases characterized by necrotic cell death, which intrinsically read upon amnesia and Alzheimer's (see above).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 6 and 7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/635,696.

The instantly claimed invention and the invention claimed in Application '696 are both drawn to a method of treating or preventing neurodegenerative diseases and/or postlesional diseases (such as Alzheimer's disease, in both cases) comprising administering an effective amount of a proline derivative of formula (I) including the specific species cinnamoyl-L-glycyl-L-phenylalanyl-L-prolinamide. Further, the instantly claimed method encompasses and/or is encompassed by the claimed method of Application '696.

Applicant indicates that a postlesional disease of toxic origin is not the same as a neurodegenerative disease and does not encompass Alzheimer's disease or amnesia, and provides as evidence the WHO classification, which separates out Alzheimer's disease from postlesional diseases of toxic origin. The Examiner has carefully considered Applicant's arguments, but such arguments are not deemed persuasive because -as stated above and cited in the previous Office Action- Alzheimer's disease, as referenced by Kan (Eur J Med Chem, 1992) is known in the art to be associated to brain lesions (amyloid B-protein plaques) whose density correlates with the severity of the disease and whose composition is toxic for mature neurons and brain regions (see, e.g., page 565, column 2 and page 566, column 1). Therefore, based upon the reference teachings, Alzheimer's disease can be classified as a postlesional disease of toxic origin.

This is a <u>provisional</u> obviousness-type double patenting rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcela M Cordero Garcia

Marcela M Cordero Garcia
Patent Examiner
Art Unit 1654

MMCG 05/05

CHRISTOPHER R. TATE
PRIMARY EXAMINER